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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT		ATTY. DOCKET NO.
08/607,419	02/26/96	FELDMANN	M	MIR92-01A3

EXAMINER	
GAMBEL, P	
ART UNIT	**PAPER NUMBER**
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DATE MAILED: 12/09/97

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☑ Responsive to communication(s) filed on 9/8/97

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☑ Claim(s) 15-30 is/are pending in the application.
Of the above, claim(s) _____ is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☑ Claim(s) 15-30 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☑ Notice of Reference Cited, PTO-892
☑ Information Disclosure Statement(s), PTO-1449, Paper No(s). 6
☐ Interview Summary, PTO-413
☐ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

--SEE OFFICE ACTION ON THE FOLLOWING PAGES--

* U.S. GPO: 1998-421-632/40206

DETAILED ACTION

1. Applicant's amendment, filed 9/8/97 (Paper No. 8), is acknowledged.
Claims 1-14 and 31-45 have been canceled.
Claims 15-16, 23-24 and 26-29 have been amended.

Claims 15-30 are pending and being acted upon presently.

2. The text of those sections of Title 35 USC not included in this Action can be found in a prior Office Action.

This Office Action will be in response to applicant's arguments, filed 9/8/97 (Paper No. 8).
The rejections of record can be found in the previous Office Action (Paper No. 5).

3. Applicant disagrees with the examiner's position on applicant's claim for priority for the instant application set forth in Paper No. 5; however, applicant asserts that the examiner's observations is believed to be moot in light of the amendment to the claims. Applicant directs support for the instant claims to USSN 08/403,785, which is the U.S. national phase application of PCT/GB93/02070, filed 10/6/93. Although applicant claims priority to USSN 07/958,248; it appears that applicant is relying upon 10/6/93 as the priority date which is being relied upon in the instant application. Priority USSN 08/403,785 was not available to the examiner at this time, therefore the examiner could not determined what the filing date of the instant claims as amended. In the interest of compact prosection, the examiner will rely upon the priority date of 10/6/93 as the priority date of the instant claims as asserted by applicant, which is subject to review upon the availability of USSN 08/403,785, which is the U.S. national phase application of PCT/GB93/02070, filed 10/6/93. The examiner apologizes for any inconvenience to applicant in examiner's inability to obtain USSN 08/403,785 at this time to verify applicant's priority date for the instant claims.

4. Applicant's IDS, filed 6/12/96 (Paper No. 6), is acknowledged.

5. Applicant will file formal drawings no later than in response to the Notice of Allowance.

6. Upon reconsideration of applicant's amended claims drawn to treating arthritis and Crohn's disease and arguments, filed 9/8/97 (Paper No. 8); the previous rejection under 35 U.S.C. § 112, first paragraph, has been withdrawn.

7. Upon reconsideration of applicant's amended claims and arguments, filed 9/8/97 (Paper No. 8); the previous rejection under 35 U.S.C. § 112, first and second paragraphs, in the recitation of "tumor necrosis factor-mediated disease", TNF "antagonist" and "a receptor molecule which binds to tumor necrosis factor" have been withdrawn.

8. Upon reconsideration of applicant's amended claims and arguments, filed 9/8/97 (Paper No. 8); the previous rejection under 35 U.S.C. § 112, second paragraph, has been withdrawn.

9. Upon reconsideration of applicant's amended claims and arguments, filed 9/8/97 (Paper No. 8); the previous rejection as it would apply to the instant claims under 35 U.S.C. § 102(a)(b) as being anticipated by Williams et al. (PNAS, 1994; 1449, #AX) has been withdrawn.

10. Upon reconsideration of applicant's amended claims, filed 9/8/97 (Paper No. 8); the previous rejection as it would apply to the instant claims under 35 U.S.C. § 103 as being unpatentable over Williams et al. (PNAS, 1994; 1449, #AX), Steinman et al. (U.S. Patent No. 4,695,459), Bender et al. (U.S. Patent No. 5,317,019) and Celltech (WO 92/07585; 1449, AN) in view of Elliott et al. (Arthr. Rheum., 1993; 1449, #AS3), Elliott et al., (Lancet , 1994; 1449, #AT3), Flesch et al. (Blood, 1992), Kay et al. (WO 92/08474; 1449, #AM), Brahn et al. Arthritis Rheum, 1992), Thorbecke et al. (PNAS, 1992), Piguet et al. (Immunol., 1992) and Heinemann et al. (U.S. Patent No. 5,502,066) or Bianco et al. (U.S. Patent No. 5,580,873) has been withdrawn.

11. Applicant's arguments, filed 9/8/97 (Paper No. 8), concerning the prior art of record have been rendered moot in view of the New Grounds of Rejection set forth below.

Applicant has argued that none of the references alone or in combination teach or suggests with a reasonable expectation of success, co-administration of cyclosporin and the administration of either a $CD4^+$ antagonist or an anti-TNFα antibody or other TNFα-specific antagonists to an individual for treating rheumatoid arthritis or Crohn's disease. Since the instant claims do not recite a $CD4^+$ antagonist, applicant's reliance and assertions concerning this specificity are rendered moot. Applicant acknowledges the therapeutic effect of combination therapy with anti-TNFα antibody and cyclosporin in Examples 4-6 of the instant specification and asserts that the magnitude of these results would not have been predictive from the cited references. Applicant asserts that nothing in the record would lead the ordinary artisan to conclude that a dramatic improvement would be expected b combination therapy with an anti-TNFα antibody.

To make the position of record clearer that combination therapy including TNFα-specific antagonists in combination with art-recognized cyclosporin therapy would have been obvious to one of ordinary skill in the art at the time the invention as made with an expectation of success; New Grounds of Rejection employing Le et al. (U.S. Patent No. 5,656,272) and Aggarwal et al. (U.S. Patent No. 5,672,347) have been applied as primary references. The combination of references clearly teach combination therapy employing both cyclosporin and TNFα-specific antagonists to an individual for treating rheumatoid arthritis or Crohn's disease.

Also, it is noted that page 72, paragraph 1 of the instant specification discloses that treatment with cyclosporin A in conjunction with anti-TNF antibody provides a greater degree of protection against arthritis than treatment with either reagent alone. These results show that there is an additive or synergistic ameliorative effect between cyclosporin A and anti-TNF antibody, based upon a collagen - induced murine model. Applicant states that is now well settled that significant improvements can rebut a prima facie case of obviousness. See In re Kollman, 201 USPQ 193 (CCPA 1979) and MPEP 716.02. Although there is a greater degree of protection in said combination therapy in a murine arthritis model, it is not clear such an effect is unexpected in view of the contribution of both cyclosporin and TNF-specific antagonists in treating such a condition, as evidenced by the prior art. In contrast to applicant's arguments of unexpected results, the prior art similarly supports the therapeutic effects of both cyclosporin and TNF-specific antagonists and the motivation to combine said reagents in the treatment of arthritis and Crohn's disease. Applicant's arguments are not found persuasive given the teachings and examples provided by the combination of references in the New Grounds of Rejection set forth below

12. Claims 15-29 are rejected under 35 U.S.C. § 103 as being unpatentable over Le et al. (U.S. Patent No. 5,656,272) OR Aggarwal et al. (U.S. Patent No. 5,672,347) OR Celltech (WO 92/07585; 1449, #AN) in view of Markowitz et al. (J Ped. Gastroenterology and Nutrition, 1991), Brahn et al. (Arthritis Rheum, 1992), Thorbecke et al. (PNAS, 1992), Piguet et al. (Immunol., 1992), Cohen et al. (Rev. Esp. Rheumatol., 20 Suppl 1:148 (1993), Abstract 318; see 1449, #AR3), Pasca et al. (Rev. Esp. Rheumatol., 20 Suppl 1:148 (1993), Abstract 319; see 1449, #AR3) and Heinemann et al. (U.S. Patent No. 5,502,066) or Bianco et al. (U.S. Patent No. 5,580,873).

The instant claims are drawn to methods of treating arthritis and Crohn's disease with cyclosporin and TNF-specific antibodies.

Le et al. teach the use of TNF-specific antagonists including the instant cA2 antibody to treat inflammatory diseases including arthritis, Crohn's pathology and ulcerative colitis (see entire document, including Therapeutic Administration in columns 35-38, Examples XX-XXIII in columns 58-79). Even though the particular patient populations employed in the referenced clinical trials were refractory to standard disease modifying anti-rheumatic drugs, it would have been obvious to the ordinary artisan that the combination of art-recognized cyclosporin treatment in combination with a highly effective TNF antagonist such as cA2 would be similarly effective for treating patients with inflammatory conditions already being treated with art recognized cyclosporin as well as a TNF antagonist. Also, Le et al. teaches that the anti-TNF peptides and/or mAbs of their invention can be administered either as individual therapeutic agents of in combination with other therapeutic agents (see column 35, lines 25-32).

Aggarwal et al. teaches the use of TNF antagonists including TNF-α-specific antibodies and analogues to treat various inflammatory conditions including arthritis and Crohn's disease (see entire document, including overlapping paragraph of columns 6-7). Aggarwal et al. also teach that the TNF antagonist can be administered in conjunction with other anti-inflammatory agents used in or proposed, including cyclosporin, for the treatment of individual immmunoinflmmatory conditions as appropriate (column 7, lines 60-67). Here, TNF antagonists when employed together with other anti-inflammatory agents, these agents may be employed in lesser dosages than when used alone. Although this reference does not teach the particular cA2 specificity per se, Aggarwal et al. clearly teaches the use of TNF-α antagonist to treat inflammatory conditions encompassed by the claimed invention. In addition, Aggrarwal et al. teaches the art known advantages of combination therapy, wherein the ordinary artisan can take advantage of two or more therapeutic agents to treat the same disease and that, in some instances, this combination permits one agent to be used in lesser amounts, thereby counteracting any toxic effects,

Celltech teaches the use of TNF-specific antibodies and xanthine derivatives such as pentoxifylline in the treatment of TNF-mediated inflammation including arthritis (see entire document).

Markowitz et al. teaches targeting TNF (page 413) and the use of cyclosporin (page 418-419) in the treatment of inflammatory bowel diseases (see entire document)

Brahn et al. teaches the use of cyclosporin to inhibit TNF-mediated arthritis (see Abstract).

Thorbecke et al. and Piguet et al. both teach the use of soluble TNF receptor in the treatment of arthritis (see entire documents).

Cohen et al. and Pasca et al. teach the use of cyclosporin and methotrexate to treat refractory rheumatoid arthritis.

Heinemann et al. and Bianco et al. both teach the use of other drugs concomitant with the reduction of TNF-mediated disease including thalidomide and xanthine derivatives such as pentoxifylline (see entire document).

Therefore, the prior art taught the claimed TNF-specific antagonists, cyclosporin and phosphodiesterase inhibitors as well as their combinations; therefore it would have been obvious to one of ordinary skill at the time the invention was made to make various combinations of said inflammatory antagonists to achieve the same desired goals in treating arthritis and Crohn's disease. diminished TNF activity to suit the nature of the therapeutic regimen. The combination of references provide an expectation of success in combining various compositions to form a third composition to most effectively induce the appropriate immunosuppression for a targeted condition.

One of ordinary skill in the art at the time the invention was made would have been motivated to combine targeting the different elements contributing to inflammatory responses including those associated with arthritis and Crohn's disease. The art teaches that targeting TNF can all diminish the activity of inflammatory responses, including the use of either TNF-specific agents such as TNF-specific chimeric antibodies or an anti-inflammatory agent such as cyclosporin and xanthine derivatives. Combination therapies were well known in the art and cyclosporin, xanthine derivatives and anti-inflammatory agent such as TNF-receptors and anti-TNF antibodies were shown to be effective in vivo. It was prima facie obvious to combine two compositions each of which is taught by prior art to be useful for same purpose in order to form third composition that is to be used for very same purpose; idea of combining them flows logically from their having been individually taught in prior art. In re Kerkhoven, 205 USPQ 1069, CCPA 1980. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

13. The non-statutory double patenting rejection, whether of the obvious-type or non-obvious-type, is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent. *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Van Ornam*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); and *In re Goodman*, 29 USPQ2d 2010 (Fed. Cir. 1993).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321 (b) and © may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.78 (d).

Effective January 1, 1994, a registered attorney or agent of record may sign a Terminal Disclaimer. A Terminal Disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

14. Claims 15-30 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3 and 5-31 of copending application Serial No 08/690,775 in view of the art recognized use of immunosuppressive therapy encompassing cyclosporin and methotrexate in arthritis and Crohn's diseases and xanthine derivatives in the treatment or reduction of TNF-mediated diseases, as set above in section 12. For example, Markowitz et al.(J Ped. Gastroenterology and Nutrition, 1991) discloses teaches targeting TNF (page 413) and the use of cyclosporin and methotrexate (page 418-421) in the treatment of inflammatory bowel diseases (see entire document). For example, Cohen et al. (Rev. Esp. Rheumatol., 20 Suppl 1:148 (1993); see 1449, #AR3); Abstract 318 and Pasca et al. (Rev. Esp. Rheumatol., 20 Suppl 1:148 (1993); Abstract 319; see 1449, #AR3) discloses the use of cyclosporin and methotrexate to treat refractory rheumatoid arthritis. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims are drawn to same or similar methods to treat inflammation, including arthritis and IBD for the reasons above.

This is a *provisional* obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

15. Claims 15-30 are directed to an invention not patentably distinct from claims 1-3 and 5-31 of commonly assigned USSN 08/690,775 because the claims are drawn to same or similar methods to treat inflammation, including arthritis and IBD, with combination therapy encompassing TNF-specific inhibitors with art-recognized therapeutic regimens for the reasons above.

Commonly assigned 08/690,775, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. § 103 if the commonly assigned case qualifies as prior art under 35 U.S.C. § 102(f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee is required under 37 C.F.R. § 1.78© to either show that the conflicting inventions were commonly owned at the time the invention in this application was made or to name the prior inventor of the conflicting subject matter. Failure to comply with this requirement will result in a holding of abandonment of the application. A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. § 103 based upon the commonly assigned case as a reference under 35 U.S.C. § 102(f) or (g).

16. Upon reconsideration of amended claims in the instant application (which does not recite anti-CD4 antibodies) and copending 08/403,785 (which is now drawn to anti-TNF antibodies and anti-CD4 antibodies and no recitation of immunosuppressives and xanthine derivatives); the previous rejections and issues associated with double patenting and common assignee have been withdrawn.

Applicant's comments, filed 9/8/97 (Paper No. 8), concerning the previous rejection and issues concerning copending USSN 08/403,785 are acknowledged. If applicant does not agree with the position set forth by the examiner above concerning the instant application and USSN 08/403,785; applicant is invited to comment and set forth its position.

17. No claim is allowed.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (703) 308-3997. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lila Feisee can be reached on (703) 308-2731. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1800 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Group 1800 by facsimile transmission. Papers should be faxed to Group 1800 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014 or (703) 308-4242.

Communications via Internet e-mail regarding this application, other than those under 35 U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to **[lila.feisee@uspto.gov]**.

All Internet e-mail communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists a possibility that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of 35 U.S.C. 122. This is more clearly set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark on February 25, 1997 at 1195 OG 89.

Phillip Gambel, Ph.D.
Patent Examiner
Group 1800
December 8, 1997